Beyond depression: the expanding role of inflammation in psychiatric disorders

That inflammation plays an important role in depression has garnered considerable attention. Nevertheless, increasing data suggest that inflammation's effects on the brain may have broad relevance to our field, contributing to symptom presentations in many psychiatric disorders beyond depression.

The link between inflammation and depression is undeniable[1]. Patients with major depression reliably exhibit increases in immune molecules that are typically associated with chronic inflammation, including inflammatory cytokines – such as tumor necrosis factor, interleukin (IL)-1 beta and IL-6 – and acute phase proteins, such as C-reactive protein (CRP)[2].

Increased inflammatory responses also exist in post-mortem brain samples of depressed individuals, with activation of inflammatory signaling pathways in brain parenchyma, trafficking of immune cells to the brain, and activation of microglia[2].

In addition, administration of inflammatory cytokines such as interferon (IFN)-alpha, or inflammatory stimuli, including typhoid vaccination and endotoxin, induce depressive symptoms. Inflammatory markers, including IL-6 and CRP, predict the development of depressive disorders[2]. Finally, blockade of inflammatory cytokines has been shown to reduce depressive symptoms, especially in patients with autoimmune and inflammatory disorders[3,4].

Although these findings support an impressive argument for a special link between inflammation and depression, increased inflammation only occurs in a subset of depressed patients, being present in 25-50% of them, depending on the sample[4,5]. Factors that contribute to increased inflammation in depression include stress, especially early life stress, metabolic factors such as obesity and metabolic syndrome, medical illnesses and their treatments, and treatment resistance[2,6]. So, at best, inflamed depressed subjects represent a depressive subtype.

Increased inflammation also exists in multiple other psychiatric disorders, including bipolar disorder, anxiety disorders, post-traumatic stress disorder (PTSD) and schizophrenia[2,7]. Thus, inflammation is agnostic to diagnosis. Indeed, when significant inflammation is present, its effects on neurotransmitters and neurocircuits contribute to specific symptom profiles that are relevant to multiple psychiatric disorders[2].

A rich body of data has documented the effects of inflammation on the brain[1,2]. Inflammatory cytokines and their downstream signaling pathways reduce monoamine availability, by decreasing the synthesis and release and increasing the reuptake of serotonin, norepinephrine and dopamine. Through effects on astrocytes and microglia, inflammatory cytokines increase the release and decrease the reuptake of glutamate, contributing to a spillover of excess glutamate outside the synapse that can bind to extrasynaptic glutamate receptors, which can lead to excitotoxicity[2].

Inflammatory cytokines also activate the kynurenine pathway, which generates neuroactive metabolites, including kynurenic acid and quinolinic acid, while also decreasing the production of growth factors, such as brain derived neurotrophic factor, contributing to a disruption of neurogenesis and ultimately synaptic plasticity[1,2].

Given that conventional antidepressants act by increasing monoamine availability, have no effects on glutamate metabolism and in part depend on neurogenesis for their efficacy, it is not surprising that inflammation is associated with treatment resistance and predicts response to alternative treatment strategies such as ketamine and electroconvulsive therapy.

The effects of inflammation on neurotransmitter systems ultimately affect neurocircuitry. Neuroimaging studies indicate that neurocircuits regulating motivation and motor activity, as well as arousal, anxiety and alarm, are reliably affected[2]. Administration of inflammatory stimuli – including IFN-alpha, typhoid vaccination and endotoxin – all reduce activity in reward-related regions of the brain, such as the ventral striatum and nucleus accumbens, an effect that is linked to decreased dopamine metabolism as well as increased basal ganglia glutamate, and is accompanied by a decreased willingness to expend effort for reward, while sensitivity to reward remains intact[2,6].

Of special relevance to psychiatric patients, endogenous inflammation as reflected by increased CRP is associated with both decreased motivation (a key component of anhedonia) and psychomotor retardation, in association with decreased functional connectivity of the ventral and dorsal striatum with the ventromedial prefrontal cortex[8]. Although less well established, data indicate that administration of inflammatory stimuli also increases the sensitivity of key brain regions involved in the assessment and response to threat, including the dorsal anterior cingulate cortex, insula, hippocampus and amygdala[7]. In addition, endogenous increases in inflammation, as reflected by CRP, correlate with decreased functional connectivity between prefrontal cortex and the amygdala, in association with symptoms of anxiety in psychiatric patients.

Of note, the effects of inflammation on these specific neurocircuits may have derived from evolutionary imperatives to promote survival in sick or wounded animals, by conserving energy resources for the immunometabolic demands of fighting infection and wound healing through behavioral withdrawal (decreased motivation and motor activity), while protecting such vulnerable animals against future attack (arousal, anxiety and alarm)[2]. Supporting this notion is the emerging understanding of the relationship between immunometabolism and cognitive processes that shape decision-making and behavioral priorities in the context of inflammation[6].

Embracing the apparent transdiagnostic relevance of increased inflammation across psychiatric disorders raises the intriguing possibility that treatments targeting inflammation and its downstream effects on the brain may have widespread applicability. Moreover, given that patients with increased inflamma-

tion can be readily identified by inflammatory biomarkers, including CRP, we are uniquely poised to target inflammation-relevant symptom clusters, notably anhedonia and possibly anxiety, across psychiatric disorders. Such strategies represent an important step toward precision medicine in psychiatry.

Nevertheless, there are limitations. If the expectation is to treat disorders as they are defined by current nomenclature, therapies targeting inflammation and its effects on the brain may fall short. For example, a recent study found that an anti-cytokine therapy to block inflammation improved symptoms of anhedonia but did not separate from placebo on overall depression scores[9]. These results suggest that, in order to fully leverage current knowledge, clinical trials and clinical practice should take into consideration both the level of inflammation and relevant symptom profiles, treating the behavioral consequences of inflammation and not the disorder; whether it is anhedonia in PTSD, symptoms of amotivation in schizophrenia, or anxiety in depression.

While at first glance this approach may run counter to current clinical practice that focuses on diagnostic entities, recognizing that different symptom profiles within diagnoses may be driven by distinct pathophysiologic processes such as inflammation can be liberating. In addition, it may encourage the field to move away from the notion of one size fits all, to a multimodal approach that addresses the many contributing factors that drive the disorders we treat.

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Inflammation affects social experience: implications for mental health

Deemed as one of the breakthrough findings of the last two decades, inflammation – the immune system's first line of defense against foreign agents – can play a role in negative mental health states such as depression. For instance, depressed individuals have higher levels of circulating pro-inflammatory markers, and experimentally increasing inflammation in healthy subjects can induce depressed mood[1].

Part of the reason why inflammation can elicit depressive symptoms is that inflammatory processes can signal the brain to initiate "sickness behavior", an adaptive response to illness which includes symptoms such as loss of appetite, fatigue and social withdrawal, bearing a striking resemblance to the hallmark features of depression.

But, is inflammatory-induced depression simply a function of the lethargy that accompanies sickness, or does inflammation actually play a distinct and larger role in the psychological and socioemotional changes that often accompany depression? Mounting evidence shows that inflammation plays a role not only in sickness behavior, but also in enhancing feelings of social disconnection and in altering sensitivity to the social world. Investigating how inflammation affects social experience may be key to better understanding the many psychiatric disorders that involve altered social sensitivity.

To explore the causal effect of inflammation on social experience, researchers have used an inflammatory challenge paradigm, in which participants are randomly assigned to receive an injection of endotoxin, a bacterial agent that triggers a time-limited inflammatory response, or a placebo injection.

In the first study to examine the socioemotional consequences of this inflammatory challenge in humans, participants exposed to endotoxin not only showed depressed mood, but also an increase in feelings of social disconnection. Moreover, enhanced feelings of social disconnection mediated the relationship between inflammation and depressed mood[1]. A subsequent study with a larger sample replicated this basic finding, and also found that inflammatory-induced feelings of social disconnection were enhanced in female participants[2].

These findings demonstrate that inflammation is a powerful organizer of social experience. But why would this be? Though it may seem surprising that the activity of the immune system could affect social experience, this unlikely pairing may provide a survival advantage. Being in a "sick" state puts an organism in a uniquely vulnerable position, and thus sensitivity to the social world may be modulated in order to help survive this vulnerable situation. Thus, for humans as well as other social species, heightened inflammation may lead to: a) a greater sensitivity to threatening social experiences in order to avoid threats to well-being during times of illness, and b) a greater sensitivity to and approach towards loved ones who could provide support and care during these times[3]. Research provides support for both of these hypothesized outcomes.

In line with the idea that inflammation increases sensitivity to negative social experience, participants who showed larger increases in inflammation in response to endotoxin also showed greater pain-related neural activity in response to social rejection[4]. Similarly, participants exposed to endotoxin (vs. placebo) showed greater pain- and threat-related neural activity in response to negative social feedback[5]. This increased sensitivity to